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TITLE: A Randomized Phase 2 Trial of 177Lu Radiolabeled Anti-PSMA Monoclonal Antibody J591 in Patients with High-Risk Castrate, Biochemically Relapsed Prostate Cancer

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14. ABSTRACT

Clinical trial has received WCMC IRB and CTSC approval with enrollment of initial 5 subjects at WCMC. An additional 33 subjects enrolled (28 treated) at participating sub-sites. Reports submitted to WCMC DSMB in July 2014 with approval to proceed without modifications.

15. SUBJECT TERMS

Prostate cancer, PSA, PSMA, monoclonal antibody, radioimmunotherapy

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I. Introduction

Men with biochemically progressive (PSA only) prostate cancer have non-radiographically apparent micrometastases that may be targeted with radioimmunotherapy. Prostate specific membrane antigen (PSMA) is the single, most well-established, highly restricted prostate epithelial cell membrane antigen known and is expressed by virtually all prostate cancers. Investigators at WCMC have generated a high-affinity antibody (J591) against the external portion of PSMA that binds to viable PSMA-expressing cells and is internalized. Studies utilizing J591 radiolabeled with Lutetium-177 (^{177}Lu) have demonstrated safety, efficacy, and accurate, selective tumor targeting in the metastatic castration-resistant prostate cancer (CRPC) setting. The physical properties of ^{177}Lu are best suited for 1-3 mm tumors (those not seen on standard imaging modalities). The hypothesis is that the addition of ^{177}Lu-J591 to ketoconazole will improve time to radiographically apparent metastases in men with biochemically progressive non-metastatic CRPC.

In this multi-center, double-blind, randomized phase II trial involving men with relapsed prostate cancer and biochemical only (PSA) progression (no radiographic evidence of metastases) despite castration at high risk of early development of metastases. The primary endpoint will be to compare the percentage of men with metastases at 18 months receiving ketoconazole plus ^{177}Lu-J591 vs ketoconazole plus trace-labeled ^{111}In-J591 (i.e. placebo). Secondary endpoints include PSA response, toxicity, progression-free survival, overall survival, the ability of radiolabeled J591 to image otherwise non-radiographically apparent metastatic sites, the prognostic and predictive capability of circulating tumor cells, baseline adrenal androgen levels, and circulating markers of hemostatic activation, fibrinolysis, and angiogenesis. With a sample size of 127 (2:1 randomization), the study will have a ≥ 0.80 power with a pre-set alpha of 5% to determine an absolute difference in 18-month metastasis free survival. An interim analysis after 12 months of follow-up will be performed and reviewed by the external DSMB (necessitating increase in sample size by 10% to 140). Stopping limits will be imposed such that a significant observed difference in the metastasis-free proportion will be grounds for the consideration of early termination of the study using an adjusted significance level corresponding to the O'Brien-Fleming group sequential rule.

II. Body

As part of the initial tasks, appropriate language incorporating the USAMRMC, ORP, and HRPO elements to the protocol was inserted and subsequently approved by the WCMC IRB and CTSC, the FDA, and ORP, delaying start of the study. Following initiation at WCMC, completion of the study has been delayed for a number of reasons which are continuing to be addressed.

Accrual to the study has been much slower than anticipated. The study was designed to target a subset of a large patient population. Though as many as 50,000 men in the U.S. per year suffer from biochemical recurrence after surgery and/or radiation, only a fraction of them meet the high risk criteria as written into the study. Based upon the science of

the treatment combined with the statistical design and the fact that several large phase III studies have recently been completed with nearly identical inclusion criteria, we believe that the basic study design should not be changed at this point. However, it is quite clear that multiple sites are required to complete the study in a timely manner. This was recognized from the start, but the length of time required to initiate additional sites has been significantly longer than expected. Despite fairly universal scientific interest in the study and initial verbal and written agreements, several sites have stalled or withdrawn due to a number of reasons. Therefore we have taken several steps to address this issue.

Based upon feedback obtained from each site that chose not to participate in the study after the start-up process had already begun, one of the main concerns has been financial worry from the institution. Sub-site investigators have generally agreed to participate based upon their enthusiasm for the study drug and the belief that they could participate in the study with better reimbursement than a NCI cooperative group study; however, many of their institutions have disagreed. The funds from the PCRP Clinical Trial Award cover only preparation of the study drug, personnel expenses at WCMC, and a fraction of the built-in correlative studies. We have been able to enhance this by 1) leveraging the award to obtain additional grant support from the Prostate Cancer Foundation, NIH (via the CTSA), additional DOD funds (via the PCCTC), and 2) by increasing philanthropic support, which is funding the additional sites. In addition, the previous Clinical Research Organization (CRO), Genexion, has been dismissed and a new CRO (Pharmatech) has been contracted and is facilitating site start-up with the initial promise of 25 subjects within 12 months at 5 sites. Should this relationship prove fruitful, it is anticipated that we will expand the contract to increase sites and subject numbers. It should be noted that WCMC and the PI have been able to leverage DOD funds via the PCMRP Clinical Trial Award with DOD funds via the PCCTC in combination with funds from the Prostate Cancer Foundation, NIH funds via the CTSA, and philanthropic funds to initiate and continue this study.It is anticipated that a limited number of sites in Europe (to be funded by a separate mechanism) will be initiated in 2015 to assist with accrual. Based upon this additional support, we have essentially been able to double the amount of per-subject reimbursement for other sites, significantly increasing interest in participation. One interesting secondary endpoint has been the ability of radiolabeled J591 to image sites of disease that were previously not apparent on standard imaging. However, because of the study design with at least a month of hormonal therapy prior to treatment/imaging and the advent of improved imaging (immuno-PET) this has become less important. As most sites are using a significant amount of their per-subject budget on this study procedure, it is important to re-consider this approach. In fact, some sites declined the study because of the cost of this scan. We are in the process of collecting all scans performed to date for an interim futility analysis. Should it be determined by our statistical team that this secondary endpoint is futile, an amendment will be submitted to drop this scan. We now have 10 active outside sites.

Overview of study sites:

- Weill Cornell Medical College: Approximately 30 pre-screen failures, 2 screen failures, 5 subjects randomized
- University of Iowa: 1 screen failure, 4 subjects randomized

- Indiana University: 1 screen failure, 13 subjects randomized
- University of Southern California: 2 screen failures, 3 subjects randomized
- Emory University – 0 screen failures, 0 subjects treated
- Cedars Sinai Medical Center – 1 screen failure, 0 subjects treated
- University of Utah – 1 screen failure, 3 subjects randomized
- University of Kansas Medical Center – 2 screen failures, 2 subjects randomized
- Georgetown University – 1 screen failures, 1 subject randomized
- University of Arizona – 1 pre-screen failure; 0 subjects treated
- UF Health (Orlando) – 1 subject randomized
- University of Pittsburg Medical Center – completing contract

SOW Task **1a**, **1b**: Additional sites are in various stages of regulatory approval:

<u>IRB Approved:</u>
- Weill Cornell Medical College
- University of Iowa
- Indiana University
- University of Southern California
- Emory University (contract in progress)
- Cedars Sinai Medical Center
- University of Utah
- University of Kansas Medical Center
- Georgetown University
- University of Arizona
- UF Health - Orlando
- University of Pittsburgh Medical Center (contract in progress)

<u>IRB Approval in progress:</u>
- Vanguard Urology, Houston, TX – budget/contract approval in process; IRB review pending

The study is currently being primarily offered via the CTSA and PCCTC groups

SOW Task **1a,b,c**: Amendments have been approved by ORP and WCMC IRB

Task **2a,b**: See above

Task **3a,b,c**: Safety lead-in phase completed, reported, reviewed by DSMB

Task **4a**: see above

Task **4b**: Weekly email communication with sites, phone/teleconferences on a regular basis.

Task **4c**: Ongoing IRB and FDA updates; last full DSMB submission July 2014.

Additional plans for recruitment: One of the most common reasons for ineligibility is the requirement to fall into the high-risk group based upon PSA kinetics or high absolute value. Many potential subjects may not be eligible at initial evaluation, but could become eligible at future time points. At WCMC, a new protocol is being submitted to the Clinical Study Evaluation Committee with the plan to submit to the IRB upon approval. This study will help us track patients with castration-resistant, biochemically recurrent prostate cancer on a prospective basis. We expect that this prospective registry will "feed" our ^{177}Lu-J591 randomized study. We have been in discussion with several of the lower accruing sites. In addition to obtaining a HIPAA waiver for pre-screening and establishing a "pre-screening log" designed to allow potential subjects to be followed, we will also be able to analyze data on pre-screen "failures". The PI has plans to travel to lower accruing sites to additionally identify reasons for low accrual, meet with study team members to discuss strategies to increase accrual, and to deliver a scientific lecture to members of institution at a forum such as grand rounds or tumor board which will highlight the study and increase referrals. Organizations such as the PCF have recognized the merit of our approach and are highlighting this study (see attachment).

III. Key Research Accomplishments

Recurrent prostate cancer is a significant problem and the development of metastatic disease is associated with morbidity and mortality. Prostate specific membrane antigen is the single most well-established, highly specific prostate epithelial cell membrane antigen known. It is highly over-expressed in the castrate state, and is accurately targeted by J591. Systemic radionuclide therapy has recently been approved for men with symptomatic metastatic CRPC to bone (Rad223, Xofigo ®) leading to excitement within the field. A more tumor-targeted approach utilizing J591 is of increased importance. The recent publication of our prior multicenter phase II study of ^{177}Lu-J591 in men with metastatic CRPC in *Clinical Cancer Research* (attached) has generated renewed scientific and clinical interest. In addition, recent studies utilizing J591-based immuno-PET imaging providing additional evidence that micrometastatic sites of disease can be identified by J591 have reinforced our hypothesis. One potential drawback of this approach is the theoretical long-term toxicity due to radiation to bone marrow. Our recent publication which evaluated long-term follow up after anti-PSMA radioimmunotherapy with radiolabeled J591 provides additional safety data (attached).

- The protocol has been approved by the WCMC IRB and CTSC as well as ORP, 11 investigational sites activated as of September 2014
- WCMC has contracted Pharmatech to assist with identification of additional sites and facilitate regulatory start-up and patient enrollment (committed to patient enrollment of 25 per year).
- A subject recruitment advertisement has been approved by the WCMC IRB and have received assistance from the Prostate Cancer Foundation, with success via increase in exposure and referrals following a press release in December, 2013. Plans are to utilize these approved "ads" in collaboration with personnel at each active site. The Study Chair will be visiting slow enrolling sites to increase enrollment.

IV. Reportable Outcomes

Kaur G, Ireland A, Christos P, Mikhail M, Chapin J, Nanus DN, **Tagawa ST**. Plasma markers of hemostatic activation, fibrinolysis, and angiogenesis in prostate cancer and advanced solid tumors: relationship to stage and prognosis. *Thrombosis Res* 2014; 133 (Suppl 2): S180, Abst OC-04

Kaur G, Ireland A, Christos P, Mikhail M, Chapin J, Nanus DN, **Tagawa ST**. Plasma markers of hemostatic activation, fibrinolysis, and angiogenesis in prostate cancer and advanced solid tumors: relationship to stage and prognosis. Plenary Session 2, 7th International Conference on Thrombosis and Hemostasis Issues in Cancer, Bergamo, IT, May 2014

Tagawa ST, Whang YE, Kaur G, Vallabhajosula S, Christos PJ, Nikolopoulou A, Jhanwar Y, Sheikh A, Ireland A, Garcias-Espana C, Goldsmith SJ, Beltran H, Bander NH, Nanus DM. Phase I trial of docetaxel/prednisone plus fractionated dose radiolabeled anti-prostate-specific membrane antigen (PSMA) monoclonal antibody 177lu-J591 in patients with metastatic, castration-resistant prostate cancer (mCRPC). J Clin Oncol 32:5s, 2014 (suppl; abstr 5064)

Tagawa ST, Whang YE, Kaur G, Vallabhajosula S, Christos PJ, Nikolopoulou A, Jhanwar Y, Sheikh A, Ireland A, Garcias-Espana C, Goldsmith SJ, Beltran H, Bander NH, Nanus DM. Phase I trial of docetaxel/prednisone plus fractionated dose radiolabeled anti-prostate-specific membrane antigen (PSMA) monoclonal antibody 177lu-J591 in patients with metastatic, castration-resistant prostate cancer (mCRPC). Poster Presentation, American Society of Clinical Oncology 2014 Annual Meeting, Chicago, IL

V. Conclusions

Biochemical relapse is common after local therapy for prostate cancer. Based on the physical properties of ^{177}Lu and the disease targeting ability of J591, ^{177}Lu-J591 is ideally suited to make a significant impact on this state of disease. The protocol has been approved and activated at the initial sites and progress continues at additional sites.

VI. References

Attached

VII. Appendices

Attachment 1: Kaur et al, *Thrombosis Res* 2014*;* 133 (Suppl 2): S180, Abst OC-04

Attachment 2: Kaur et al, Plenary Session 2, 7th International Conference on Thrombosis and Hemostasis Issues in Cancer, Bergamo, IT, May 2014

Attachment 3: Tagawa et al, *J Clin Oncol* 32:5s, 2014 (suppl; abstr 5064)

Attachment 4: Tagawa et al, Poster Presentation ASCO 2014 Annual Meeting

Attachment 5: PCF research highlight, March 2014

Attachment 6: Approval documents: (a) Most recent WCMC IRB approval document

multivariate analyses were performed to identify independent VTE predictors.
Results: From June 2010 to June 2013, 1,322 ambulatory patients were evaluated for a new diagnosis of cancer; 13 on oral anticoagulation at the moment of enrollment were excluded from the analysis leaving 1,309 patients for evaluation. Complete follow up was available for the whole population. The mean age of the study population was 62.3 years, and 63% of patients were men; 897 patients (68.5%) were on chemotherapy. At the end of follow up, 66 patients (5.04%) had a VTE. At the univariate analysis among the traditional cardiovascular risk factor smoking and hypertension were significantly associated with an increased VTE risk (OR 2.45, 95% CI 1.31, 4.59 and 1.63, 95% CI 1.00, 2.66 respectively) whereas DM, obesity and dyslipidemia were not. Furthermore, age, previous VTE, very high risk cancer type (stomach and pancreas) and presence of metastasis were significantly or marginally significant associated with an increased risk of VTE (p <0.10). At the multivariate analysis only previous VTE and very high risk cancer type remained significantly associated with an increased risk of VTE (OR 13.77, 95% CI 6.94, 27.34 and 2.31, 95% CI 1.29, 4.13 respectively) whereas association with all the other variables including smoking and hypertension disappeared. Results of subgroup analyses including only patients undergoing chemotherapy during follow up period gave similar results (data not shown).
Conclusions: The role of traditional cardiovascular risk factors in the pathogenesis of cancer related VTE appeared limited. Other studies are necessary to confirm our preliminary findings.

Plenary Session 2: Hypercoagulability in cancer / Biomarkers for VTE

OC-03
Circulating microparticles of glial origin and tissue factor bearing in high-grade glioma: further evidence of a prothrombotic role

C.M. Radu[1], M.T. Sartori[1], E. Campello[1], P. Ciccarino[2], A. Della Puppa[2], L. Spiezia[1], R. Scienza[2], P. Simioni[1]
[1]Department of Cardiologic, Thoracic and Vascular Sciences (DCTV), 2nd Chair of Internal Medicine, Coagulation Diseases Unit, [2]Neurosurgery, Department of Neurosciences; University of Padua; Padua, Italy.

Introduction: Glioblastoma multiforme (GBM) showed increased plasma levels of glial-derived and prothrombotic tissue factor (TF)-bearing microparticles (MP).
Aim: To evaluate (1) the presence of circulating levels of glial-derived and TF-bearing MP in GBM patients compared to both meningioma patients and healthy subjects, (2) the cellular origin of TF-bearing MP, (3) whether basal level of MP is predictive of venous thromboembolism (VTE) complications, and (4) the possible role of MP as a predictive biomarker of disease progression.
Material and Methods: Fifteen patients with GBM (M/F: 7/8; median age 64 [41-76] years) and 10 patients with meningioma (M/F: 5/5; median age 66 [45-79] years) who consecutively underwent surgery were prospectively enrolled. Twenty-five age- and gender-matched healthy controls were recruited in the same period. In-hospital and follow-up data were collected prospectively 1, 4, and 7 months after the diagnosis. All patients underwent radiation and concomitant adjuvant chemotherapy with temozolomide. MP were identified by size and annexin V-FITC labeling, using flow-cytometry. Glial-derived MP (GFAP+) were measured using anti-glial fibrillary acidic protein (GFAP)-FITC and TF-bearing (TF+ MP) using anti-CD142-PE. To explore the possible leukocyte, endothelial and platelet cellular origin of TF+MP, we tested the samples by double labeling for TF and anti-CD62L (L-Selectin+), anti-CD62E (E-Selectin+), and anti-CD62P (P-Selectin+) antibodies, respectively.
Results: Circulating levels of GFAP+MP were significantly higher in GBM patients (median 82 [55-91] MP/μL) than in meningioma patients (41 [30-53 MP/μL, p=0.006] and in controls (40 [31-53] MP/μL, p<0.001). TF+MP were significantly higher both in GBM (116 [101-139] MP/μL) and in meningioma (117 [109-136] MP/μL) than in healthy controls (66 [17-87] MP/μL; both p<0.001). GBM patients showed significantly higher levels of TF+/L-Selectin+ (56 [49-60] MP/μL) and TF+/E-Selectin+ (106 [86-125] MP/μL) than controls (14 [11-25] MP/μL, p<0.01; 33 [20-42] MP/μL, p<0.01). Five GBM patients developed VTE during follow-up (33%). They had significantly higher median baseline levels of TF+ MP (134 [118-141] MP/μL) than patients who experienced no VTE (108 [97-115] MP/μL, p<0.01). GBM patients with basal high levels of TF+ MP (above the 95th percentile calculated on controls) had an unadjusted RR for VTE of 3.98 (95% CI, 1.69 to 8.03). Eight GBM showed disease progression during follow-up period (53%). They presented basal median levels of GFAP+ and TF+MP significantly higher than patients with stable disease (both p<0.01).
Conclusions: Glial-derived MP were significantly increased in GBM patients and seemed to be specific for this malignancy. TF+MP were increased both in GMB and in meningioma, and co-expressed marker of endothelial and leukocyte-origin. In GBM patients TF+MP were significantly associated with the development of VTE complications and likely predictive of a worse prognosis.

OC-04
Plasma markers of hemostatic activation, fibrinolysis, and angiogenesis in prostate cancer and advanced solid tumors: relationship to stage and prognosis

G. Kaur, A. Ireland, P. Christos, M. Mikhail, J. Chapin, D. Nanus, S. Tagawa
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Introduction and Aim: Thrombosis and hemostasis as well as angiogenesis may be clinically involved in the setting of malignancy. Subclinical activation of these systems may be assayed in plasma, and levels of proteins may be related to stage and/or prognosis.
Materials and Methods: Plasma was prospectively collected via non-traumatic peripheral venipuncture in sodium citrate-containing vacutainer tubes in patients (pts) without history of prior venous thromboembolism (VTE) or current anticoagulation prior to treatment in 5 cohorts of pts following IRB approval: 1) clinically localized prostate cancer (PC) prior to prostatectomy; 2) biochemically recurrent, non-metastatic PC prior to hormonal therapy (BRPC); 3) castration-resistant, non-metastatic PC (M0 CRPC); 4) advanced PC prior to hormonal therapy (APC); 5) metastatic, refractory non-prostate solid tumors (AST). Platelet-poor plasma was assayed by ELISA for D-dimer (DD), thrombin anti-thrombin complex (TAT), IL-6, IL-8, vascular endothelial growth factor (VEGF), and tissue factor (TF).
Results: 217 subjects were accrued with baseline marker values available in the majority except for TF (Table 1). Within prostate cancer cohorts, median levels of markers increased with recurrence and increased stage. Compared to the reference (pre-prostatectomy), DD was higher in APC (p=0.001), TAT higher in all other groups (p<0.0001), IL-6 higher in BRPC and APC (p<0.0001), IL-8 higher in BRPC and APC (p<0.0001), VEGF higher in APC (p=0.004). The AST group had higher levels of markers, even compared to advanced PC (DD p=0.037, TAT p=0.013, IL-6 p=0.034, IL-8 p<0.0001). For the entire group, levels of DD, IL-6, IL-8, and VEGF were prognostic for overall survival (p<0.0001 for each). As most of the deaths were driven by the advanced groups and to control for stage (metastatic vs. non-metastatic), the advanced disease cohorts (APC and AST) were combined and analyzed. Markers were prognostic when analyzed as continuous variables (all p values < 0.01) as well as when dichotomized by median values, with hazard ratios (HR) for death as follows: DD HR 4.55 (p=0.001); TAT HR 7.38 (p=0.002); IL-6 HR 7.85 (p=0.001); IL-8 HR 33.10 (p<0.0001); VEGF HR 3.23 (p=0.028); TF was not prognostic.

Conclusions: Activation of the hemostatic and fibrinolytic systems and angiogenesis is common in cancer and generally increases with more advanced stages of prostate cancer and in advanced solid tumors. Increased hemostatic activation, fibrinolysis, and angiogenesis can be measured in peripheral blood and is prognostic for overall survival.

Table 1

Cohort	PC	BRPC	M0 CRPC	APC	AST
n	153	12	9	29	14
DD					
n	143	12	5	28	6
median	221.13	260.60	450.20	413.90	1423.05
TAT					
n	153	12	6	28	6
median	1.87	3.80	13.19	3.25	5.77
IL-6					
n	153	12	-	28	10
median	1.39	3.12	-	3.12	10.08
IL-8					
n	153	-	6	-	8
median	12.31	-	6.15	-	32.99
VEGF					
n	126	12	6	28	10
median	22.00	20.55	18.55	21.75	65.10
TF					
n	0	12	6	28	-
median	-	24.00	13.19	25.00	-

Plenary Session 3: Bleeding complications, microangiopathies and thrombocytopenias

OC-05
Clinical evidence for a link between microparticle-associated tissue factor activity and overt disseminated intravascular coagulation in patients with acute myelocytic leukemia

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Medical University of Vienna, Austria

Introduction: Recently, Gheldof and colleagues found that highly procoagulant microparticles (MPs) are released from the NB4 acute promyelocytic cell line. A large part of these MPs expressed tissue factor (TF) in addition to phosphatidylserine on the surface [1].
Aim: We determined MP-TF activity levels in AML patients with- or without overt disseminated intravascular coagulation (DIC) or acute venous thromboembolism (VTE) to investigate the role of TF-bearing MPs in AML-related coagulation disorders.
Methods: MP-TF activity was measured according to a standardized protocol for a chromogenic MP-TF-dependent factor Xa generation assay. Seven patients with AML were included: 2 patients had overt DIC, 3 patients had acute VTE and 2 patients neither had DIC nor VTE.
Results: We detected highly elevated MP-TF activity (4.43 pg/mL and 3.16 pg/mL, respectively) in the 2 AML patients with overt DIC, which decreased to 0.1 pg/mL and 0.0 pg/mL, after cessation of DIC. In the other AML patients MP-TF activity was low. D-dimer levels were highly elevated in the two AML patients with overt DIC (D-dimer: 57.71 μg/mL and 51.63 μg/mL, respectively) and 19-fold increased compared to the other patients. Only in these two AML patients the percentage of blast cells in the peripheral blood smear was high (20% and 32%, respectively). MP-TF activity, D-dimer, thrombocyte count and fibrinogen levels during the course of DIC are shown for the two patients with overt DIC (Figure 1A and 1B).
Conclusions: In this study we demonstrate that MP-TF activity is highly elevated during AML-related overt DIC and low after cessation. To our surprise MP-TF activity was low in AML patients with acute VTE.

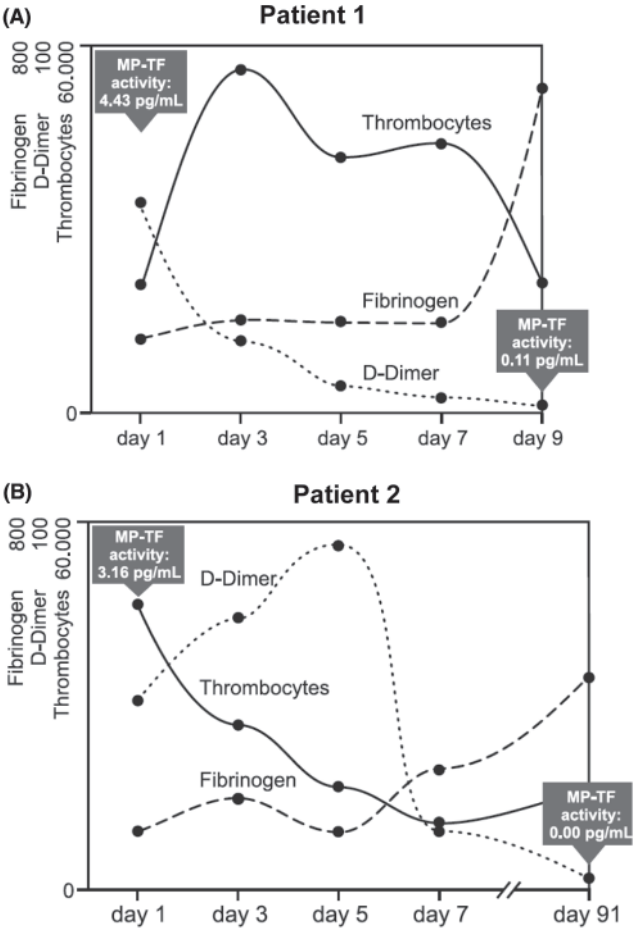

Fig. 1.

Our clinical data strongly supports the experimental data by Gheldof and colleagues. Taken together, these two studies provide strong evidence for a determining role of TF-bearing MPs in the pathogenesis of overt DIC in patients with AML.

Reference:

[1] Gheldof D, Mullier F, Bailly N, Devalet B, Dogne J, Chatelain B, et al. Microparticle bearing tissue factor: A link between promyelocytic cells and hypercoagulable state. Thromb Res 2014;133:433-9

OC-06
Fatal pulmonary embolism and fatal bleeding in cancer patients with venous thromboembolism receiving anticoagulation

B. Zalunardo[1], D. Farge-Bancel[2], J. Trujillo-Santos[3], P. Debourdeau[4], A. Bura-Riviere[5], E.M. Rodriguez-Beltrán[6], P. Di Micco[7], A. Visonà[1], D. Zeltser[8], M. Monreal[9], and the RIETE Investigators
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Introduction: Guidelines recommend similar antithrombotic therapy for cancer patients with pulmonary embolism (PE) or deep vein thrombosis (DVT), even though their natural history has not been thoroughly studied.

Plasma markers of hemostatic activation, fibrinolysis, and angiogenesis in prostate cancer and advanced solid tumors: Relationship to stage and prognosis

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Disclosures for Scott T. Tagawa, MD, MS

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Background

- Carcinoma has long been associated with thrombotic and hemostatic complications
- Cancer + VTE is associated with poorer overall survival
- Even in the absence of overt thrombosis, many patients with cancer have elevated plasma markers of hemostatic activation and fibrinolysis
- Inflammatory and angiogenic systems are closely linked to hemostasis/fibrinolysis

Bouillaud, Arch Gen Med 1823
Trousseau, Clin Med Paris 1865
Blom, JAMA 2005
Chew, Arch Intern Med 2006
Levitan, Medicine 1999
Prandoni, Blood 2002
Sorensen, N Engl J Med 2000
Rickles, Cancer Metastasis Rev 1992
Rickles, Pathophysiol Haemost Thromb 2003
Donati, Pathophysiol Haemost Thromb 2003

Hypothesis

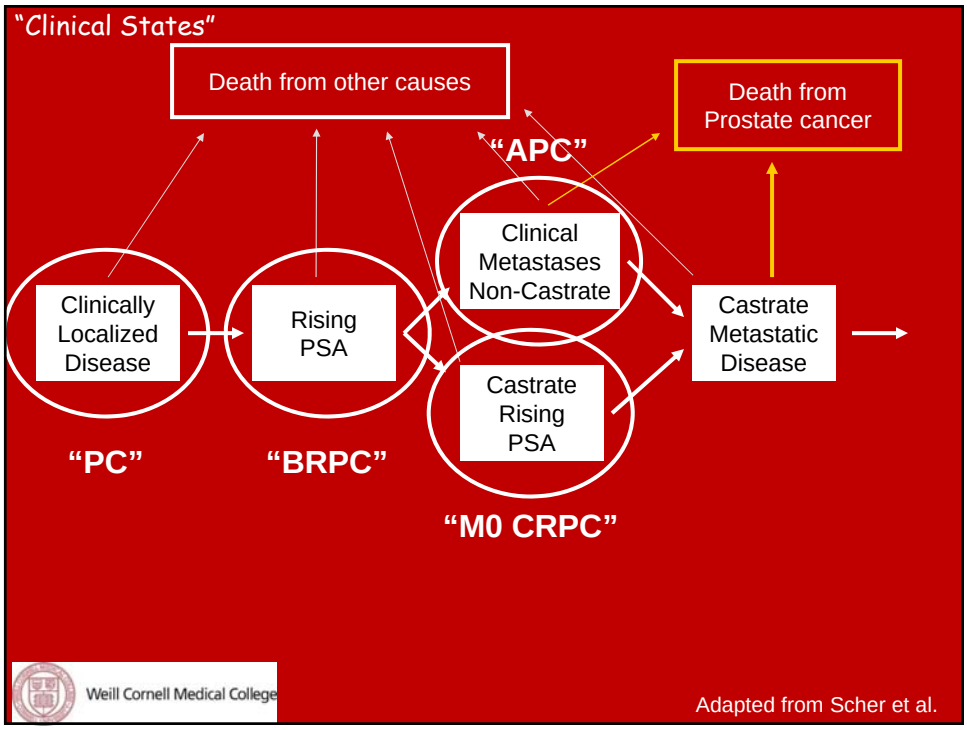
- Subjects with cancer will have detectable, often elevated plasma markers of hemostatic activation, fibrinolysis, and angiogenesis
- Levels of markers are associated with malignant disease stage
- Levels of markers are associated with prognosis

Methods: Entry Criteria

- No history of VTE, no current anticoagulation
- One of 5 cohorts prior to treatment:
  - Clinically localized prostate cancer (PC) prior to prostatectomy[1]
  - Biochemically recurrent, non-metastatic PC prior to hormonal therapy (BRPC)[2]
  - Castration-resistant, non-metastatic PC (M0 CRPC)[3]
  - Advanced PC prior to hormonal therapy (APC)[2]
  - Metastatic, refractory non-prostate solid tumors (AST)[4]

Weill Cornell Medical College

1 Tagawa et al, ICTHIC 2007 & BJUI 2008
2 Arnason et al, ICTHIC 2012
3 clinicaltrials.gov NCT00859781
4 clinicaltrials.gov NCT00967577; Pail et al AACR 2014



Methods: Entry Criteria

- No history of VTE, no current anticoagulation
- One of 5 cohorts prior to treatment:
  - Clinically localized prostate cancer (PC) prior to prostatectomy[1]
  - Biochemically recurrent, non-metastatic PC prior to hormonal therapy (BRPC)[2]
  - Castration-resistant, non-metastatic PC (M0 CRPC)[3]
  - Advanced PC prior to hormonal therapy (APC)[2]
  - Metastatic, refractory non-prostate solid tumors (AST)[4]

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1 Tagawa et al, ICTHIC 2007 & BJUI 2008
2 Arnason et al, ICTHIC 2012
3 clinicaltrials.gov NCT00859781
4 clinicaltrials.gov NCT00967577; Pail et al AACR 2014

Methods (cont)

- Platelet-poor plasma collected via non-traumatic peripheral venipuncture in 2.3% sodium citrate[1]
- Analyzed by ELISA for:
  - D-dimer (DD)
  - Thrombin-antithrombin complex (TAT)
  - Interleukin 6 (IL-6)
  - Interleukin 8 (IL-8)
  - Tissue factor (TF)[2]
  - Vascular endothelial growth factor (VEGF)

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1 – some assays in PC group with additional aprotinin, benzamidine, EDTA
2 – not analyzed in PC group

Methods (cont)

- Wilcoxon rank-sum test used to compare median baseline values across cohorts
- Median overall survival (OS) for each cohort estimated using Kaplan-Meier
- Hazard ratios for OS analyzed using log-rank (both continuous and median values used)
  - Analysis for metastatic cohorts


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Results: Demographics

- N = 217
- 208 (95.9%) men; 9 women

Cohort	PC	BRPC	M0 CRPC	APC	AST
n	153	12	9	29	14
Age					
Median	71	72	69	73	63
Range	55-89	54-88	54-86	59-93	44-88

- AST Cohort: 5 men, 9 women
  - Lung (adeno or mixed = 5), pancreatic (2), urothelial (2), 1 each: colon, GE Jxn, ovarian, renal cell, mucosal melanoma


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Results: Marker values

Cohort	PC	BRPC	M0 CRPC	APC	AST
n	153	12	9	29	14
DD					
n	143	12	5	28	6
range (ng/ml)	75.302-2010.421	105.3-2600.4	132.4-763.5	96.3-3654.4	321.9-1471
median	**221.13**	**260.6**	**450.2**	**413.9**	**1423.05**
TAT					
n	153	12	6	28	6
range (ug/ml)	1.245-12.022	0-155195	2.39-118.3	1.9-28.2	3.6-9
median	**1.87**	**3.8**	**13.19**	**3.25**	**5.77**
IL-6					
n	153	12	6	28	10
range (pg/ml)	0.303 - 6.775	0-10.51	0-4.26	0-91.83	0-38.44
median	**1.39**	**3.12**	**0**	**3.12**	**10.08**
IL-8					
n	153	0	6	0	8
range (pg/ml)	3.873-26.032	-	0-12.41	-	0-681.5
median	**12.31**	**-**	**6.15**	**-**	**32.99**
VEGF					
n	126	12	6	28	10
range (pg/ml)	5-386	15.6-47.9	18.5-36.1	14.8-181.8	0-261.4
median	**22**	**20.55**	**18.55**	**21.75**	**65.1**
TF					
n	0	12	6	28	5
range (pg/ml)	-	0-17.4	0-32.2	0-241.7	0-27.2
median	**-**	**24**	**13.19**	**25**	**0**

Results: Cohort comparison (1)

- Compared to PC (reference group)
- D-dimer
  - Prostate cancer: Increased with castration-resistance (p=0.07; n=5) and advanced disease (p<0.0001)
  - Higher in AST (p=0.001)
- TAT
  - Higher in all cohorts (p<0.0001)

Results: Cohort comparison (2)

- Compared to PC (reference group)
- IL-6
  - Increased with BRPC ($p<0.0001$) and advanced disease ($p<0.0001$)
  - Higher in AST ($p<0.0001$)
- IL-8
  - Higher in AST ($p<0.0001$)
- VEGF
  - Higher in AST ($P=0.004$)

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Results: Cohort comparison (3)

- Compared to all prostate cancer cohorts (including the advanced prostate group), very late stage disease (AST) had higher levels of:
  - D-dimer ($p=0.037$)
  - TAT ($p=0.013$)
  - IL-6 ($p=0.034$)
  - IL-8 ($p<0.0001$)

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Results: Prognosis (1)

- In univariate analysis including all subjects, as continuous variables, markers were prognostic for OS:
  - D-dimer: HR 1.001 ($p<0.0001$)
  - IL-6: HR 1.036 ($p<0.0001$)
  - IL-8: HR 1.007 ($p<0.0001$)
  - VEGF: HR 1.009 ($p<0.0001$)

Results: Prognosis (2)

- Death events driven by advanced stage pts (only 2 deaths in non-metastatic disease)
- In analysis of metastatic pts only (i.e. controlling for stage), as continuous variables, markers were prognostic for OS:
  - D-dimer: HR 1.001 ($p=0.007$)
  - IL-6: HR 1.022 ($p=0.007$)
  - IL-8: HR 1.005 ($p=0.004$)
  - VEGF: HR 1.020 ($p<0.0001$)
  - TAT: HR 1.091 ($p=0.003$)

Results: Prognosis (3)

- Prognostic value in metastatic pts dichotomized at median marker values:
  - D-dimer: HR 4.55 (p=0.01)
  - IL-6: HR 7.85 (p<0.001)
  - IL-8: HR 33.10 (p<0.0001)
  - VEGF: HR 3.23 (p=0.02)
  - TAT: HR 7.38 (p<0.001)

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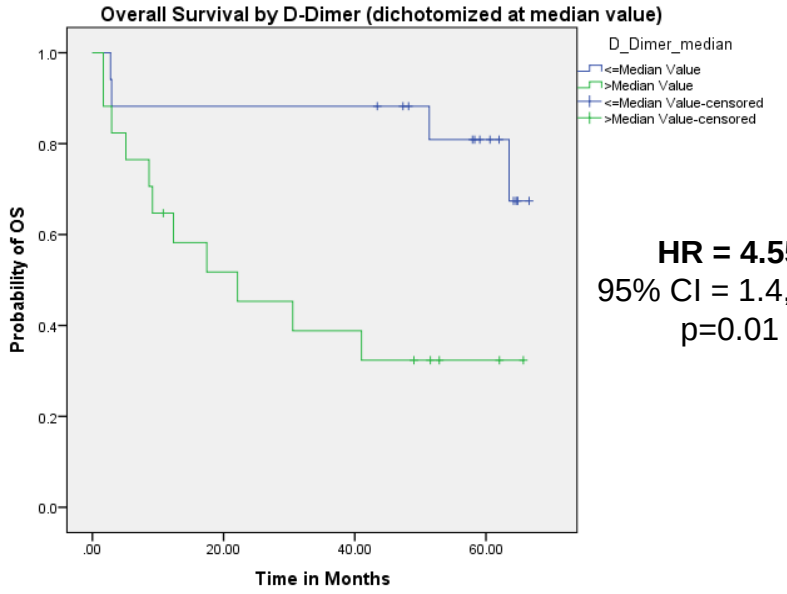

HR = 4.55
95% CI = 1.4, 14.8
p=0.01

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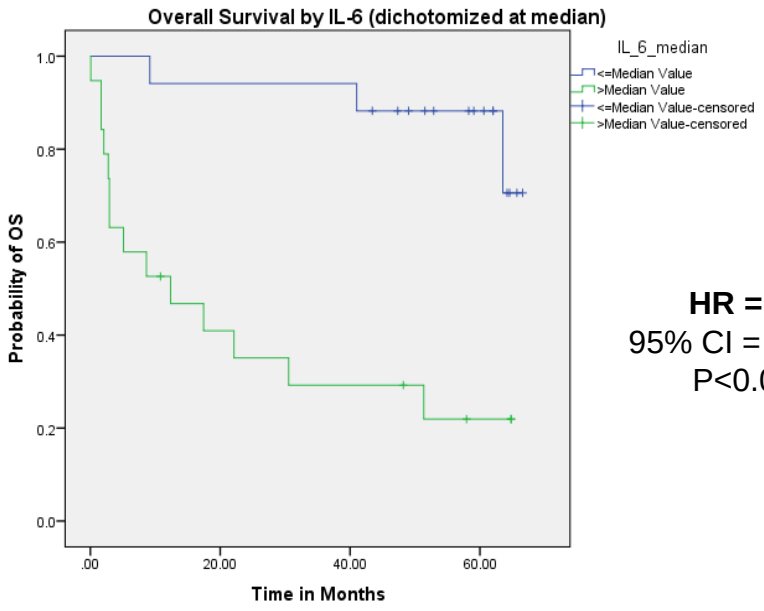

HR = 7.85
95% CI = 2.2, 27.8
P<0.0001

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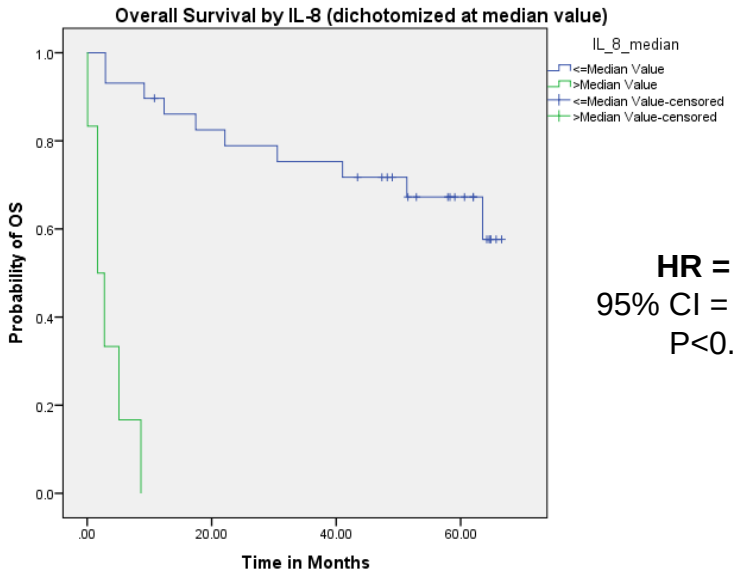

HR = 33.10
95% CI = 6.4, 171.8
P<0.0001

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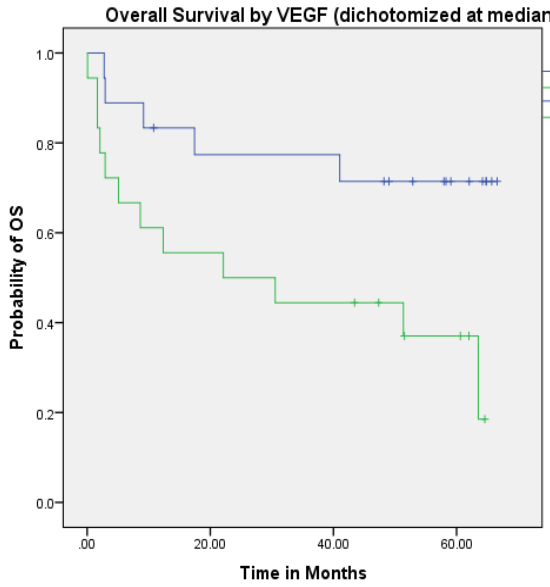

HR = 3.23
95% CI = 1.1, 9.2
P=0.02

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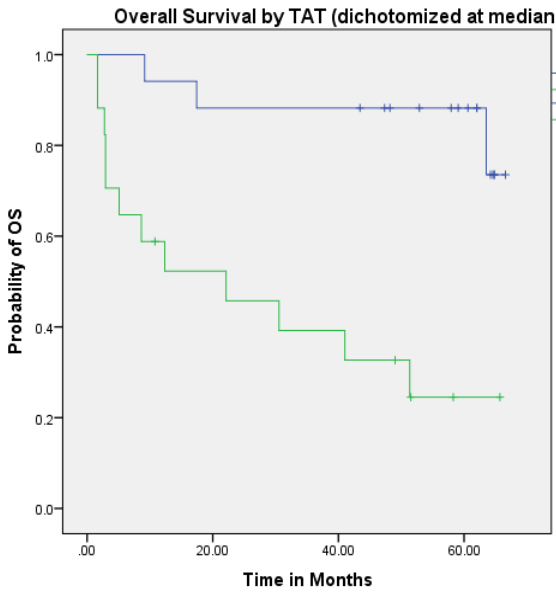

HR = 7.38
95% CI = 2.0, 26.9
P<0.0001

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Conclusions

- Consistent with hypothesis (and previous results), plasma markers of hemostatic activation, fibrinolyisis, and angiogenesis are detectable in patients with cancer
- Levels of markers are associated with stage
- Levels of markers are strongly associated with prognosis, even when controlling for stage

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PATIENTS AND THEIR FAMILIES

Why prostate cancer?

- I am a GU oncologist
- PC is the most common cancer in U.S. men, 2nd leading cause of cancer deaths
- Medicare claims: PC 3rd most common cancer associated with VTE, also associated with clinical fibrinolysis
- Subclinical activation of hemostastasis and fibrinolyisis previously demonstrated with PC
  - Higher than age-matched controls
  - Associated with surgical bleeding

Levitan, Medicine 1999 Tagnon, Cancer 1953
Kohli, Semin Thromb Hemost 2003 Tagawa BJU Int 2008
Kohli, Blood Coagul Fibrinolysis 2002

Phase I trial of docetaxel/prednisone plus fractionated dose radiolabeled anti-prostate-specific membrane antigen (PSMA) monoclonal antibody ^{177}Lu-J591 in patients with metastatic, castration-resistant prostate cancer (mCRPC).

Scott T. Tagawa, Young Whang, Gurveen Kaur, Shankar Vallabhajosula, Paul Christos, Anastasia Nikolopoulou, Yuliya Jhanwar, Arif Sheikh, Adam Ireland, Carmen Garcias, Stanley J. Goldsmith, Himisha Beltran, Neil H. Bander, David M. Nanus.

Weill Cornell Medical College, University of North Carolina Chapel Hill

Background- Docetaxel remains a standard agent for mCRPC and has radiosensitizing properties. ^{177}Lu-J591 delivered with fractionated dosing leads to less myelosuppression while maintaining efficacy in mCRPC. This study was designed to determine the safety, dose limiting toxicity (DLT) and maximum tolerated dose (MTD) of fractionated ^{177}Lu-J591 administered concurrently with standard docetaxel.

Methods- Men with progressive mCRPC received docetaxel 75 mg/m^2 every 3 weeks with escalating 2 fractionated doses of ^{177}Lu-J591 (initial dose 20 mCi/m^2 x2 up to max of 40 mCi/m^2 x2) with cycle 3. Cycle 4 of docetaxel was planned 6 weeks after cycle 3 to allow for recovery from ^{177}Lu-J591-associated hematologic toxicity. DLT was defined as delay in docetaxel >3 weeks, prolonged myelosuppression or need for >2 platelet (plt) transfusions, febrile neutropenia, or grade >2 non-heme toxicity following ^{177}Lu-J591. PSA was assessed prior to each cycle and CTC count (CellSearch) was assessed at baseline and after ^{177}Lu-J591.

Results- 15 men with median age 67.3 (range 49.2-80.8), PSA 84.3 (17-776), 73.3% with elevated LDH, 71.4% unfavorable CTC counts received up to the highest anticipated dose (40 mCi/m^2 x2). No DLT was seen at any dose level. Significant toxicity was limited to reversible myelosuppression. Gr 4 ANC without fever occurred in 3 (20%) and Gr 4 plts in 2 (13.3%), with 2 receiving prophylactic plt transfusion. No Gr >2 non-heme toxicity was reported. 13 had PSA decline, with 11 (73.3%) and 12 (80%) having >50% and >30% PSA decline respectively. All 14 evaluable men had decline (85.7%) or persistently undetectable (14.3%) CTC counts, with 78.6% having CTC counts decline by >50% and 78.6% having favorable counts after ^{177}Lu-J591. Of 10 analyzed to date, all had targeting of known sites of disease by planar ^{177}Lu-J591 imaging.

Conclusion- The combination of fractionated dose ^{177}Lu-J591 and docetaxel/prednisone is well tolerated in patients with mCRPC. Without pre-selection, accurate targeting of known sites of disease and a strong preliminary efficacy signal was observed.

Phase I trial of docetaxel/prednisone plus fractionated dose radiolabeled anti-prostate-specific membrane antigen (PSMA) monoclonal antibody ^{177}Lu-J591 in patients with metastatic, castration-resistant prostate cancer (mCRPC).

Scott T. Tagawa, Young Whang, Gurveen Kaur, Shankar Vallabhajosula, Paul Christos, Anastasia Nikolopoulou, Yuliya Jhanwar, Arif Sheikh, Adam Ireland, Carmen Garcias, Stanley J. Goldsmith, Neil H. Bander, David M. Nanus

Weill Cornell Medical College, New York, NY and University of North Carolina, Chapel Hill, NC

BACKGROUND

- J591 is a deimmunized anti-PSMA monoclonal antibody that binds to the extra-cellular domain of viable PSMA+ cells with rapid internalization
  [Liu et al, Cancer Res 1997; Liu et al, Cancer Res 1998]
- ^{177}Lu is a low energy β particle along with a gamma emission which allows imaging. The short range of its β emission is ideal for 1-3 mm tumor masses (although it may be suboptimal for bulky tumors)
  [O'Donoghue et al, J Nuc Med 2005]
- A phase II study of ^{177}Lu-J591 delivered as a single bolus demonstrated efficacy with evidence of dose-response and confirmed targeting, with predictable, reversible myelosuppression (including need for some platelet transfusions) as the main treatment emergent adverse events
  [Tagawa et al, Clin Cancer Res 2013]
- Dose fractionation may decrease toxicity while maintaining efficacy
- A phase I trial of fractionated (2-dose) ^{177}Lu-J591 confirmed the hypothesis that fractionation has less myelosuppression, with higher cumulative doses achieved with less toxicity while maintaining efficacy
  [Tagawa et al, ASCO 2010 and ECC 2013]
- Docetaxel (i.e . standard chemo for mCRPC) is a known radiosensitizer
- We hypothesized that the combination of docetaxel plus ^{177}Lu-J591 delivered in fractionated doses will be tolerated and may have better efficacy than either agent alone
- The objective of this study was to determine toxicity profile and maximal tolerated dose (MTD) of ^{177}Lu -J591 plus docetaxel.

METHODS

Entry Criteria Summary:

- Progressive castration-resistant prostate cancer
- Measureable or evaluable metastatic disease
- ECOG performance status 0-2
- Plt>150,000/mm3, ANC>2,000/mm3, Hb>10 g/dL
- Prior docetaxel sensitivity or no prior docetaxel
- Neuropathy < Gr 2

DLT Definition

- Grade > 2 mAb-attributable non-hematologic toxicity
- Grade 4 neutropenia or thrombocytopenia > 14 days
- Need for > 2 platelet transfusions or hemorrhage
- Febrile neutropenia
- > 3 week delay for docetaxel (i.e. > 9 weeks from concurrent cycle)

#DLT / #Patients	Decision
0/3	Escalate to the next higher dose
1/3	Add 3 patients at the same dose
1/6	Escalate to the next higher dose / Trial ends
³ 2/3 or ³ 2/6	Decrease dose for the next groups of patients
The MTD is defined as the maximum dose with less than 2/6 DLTs. If there are 2 or more DLTs at dose level 1, all test doses will be declared to have exceeded the MTD.	

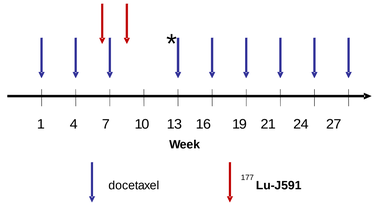
METHODS

Treatment:

- Docetaxel 75 mg/m2 q3 weeks with pause after RIT (see schema)
- 177Lu-J591 RIT combined with docetaxel cycle 3 in escalating cohorts:
  Dose level 1: ^{177}Lu-J591 at 20 mCi/m^2, dose escalation as follows:

Dose	Dose Schedule
1	20 mCi/dose
2	25 mCi/dose
3	30 mCi/dose
4	35 mCi/dose
5	40 mCi/dose

If dose level 1 without DLT, Cohort 2 would be treated at dose level 3



*Docetaxel #4 to be delivered minimum of 6 wks after docetaxel #3 and upon recovery of ANC>1500 and Plts > 100

- ^{177}Lu-J591 with cycle 3 to allow cytoreduction prior to RIT
- Initial RIT 2-3 days prior to docetaxel to optimize radiosensitization
- Following cycle 5, chemotherapy was per investigator discretion

RESULTS

Enrollment, Baseline Characteristics

- 15 subjects enrolled May 2009 – Sep 2013 at two institutions
  (3 pts in Cohort 1: 20 mCi/m^2; 4 pts in Cohort 2: 30 mCi/m^2;
  4 pts in Cohort 3: 35 mCi/m^2; 4 pts in Cohort 4: 40 mCi/m^2)

Baseline characteristics listed in Table 1 below (similar between cohorts)

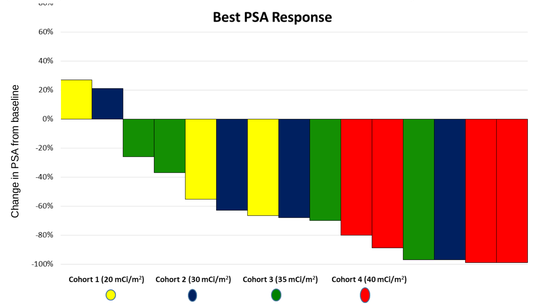
Baseline Characteristics (N=15)

Age, years		PSA (ng/mL)	
Median (range)	69.06 (49.28-80.81)	Median (range)	75.8 (3.03-776)
Gleason Sum, n (%)		LDH (IU/L)	
6	2 (13.3%)	Median (range)	231 (119-687)
7	6 (40%)	Elevated LDH, n (%)	11 (73.3%)
8 - 10	6 (40%)	Hemoglobin (g/dL)	
unknown	1 (6.6%)	Median (range)	12.5 (8.6-15.0)
Sites of Metastases		Alkaline Phosphatase (IU/L)	
Bone	14 (93.3%)	Median (range)	147 (64-1321)
Lymph Node	9 (60%)	Previous Radiotherapy	6 (40%)
Lung	1 (6.7%)	Prostatectomy	8 (53.3%)
Liver	0 (0%)	CTC Count (CellSearch), n=14	
ECOG PS		Median	24
0	5 (35.7%)	Range	0-429
1	8 (57.1%)	Favorable (0-4)	4 (28.6%)
2	1 (7.1%)	Unfavorable (5+)	10 (71.4%)

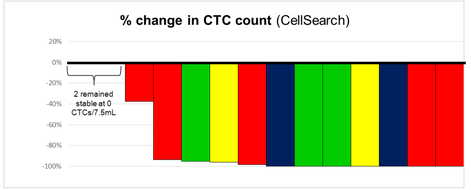
RESULTS

Anti-tumor Effects

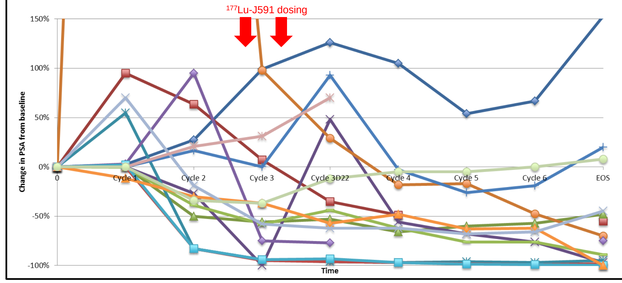
- For the entire study, 11 (73.3%) with ≥ 50% PSA decline, 13 (86.7%) any decline
- 5 (33.3%) had measurable disease: 3 PR, 1 SD, 1 PD by RECIST



- 14 of 14 evaluable men had decline or persistently favorable CTC counts
- 71.4% with unfavorable counts → 21.4% unfavorable after treatment

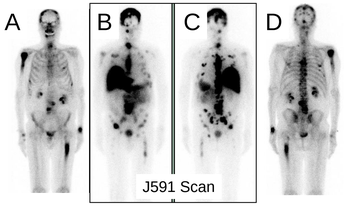


- Following ^{177}Lu-J591 93.3% had continued decline in PSA or reversal of previously rising PSA with initial docetaxel



Tumor Targeting

- ^{177}Lu-J591 imaging was performed 6-8 days following the initial dose
- As previously demonstrated, accurate tumor targeting was seen



Outer images:
Ant (A) and post (D) images of pre-treatment bony metastases on Tc-MDP bone scan

Inner images:
Ant (B) and post (C) total body images obtained via dual head gamma camera of sites of uptake 7 days after ^{177}Lu-J591 administration

(NOTE: ^{177}Lu-J591 is cleared via liver)

Toxicity

- **No dose-limiting toxicity occurred at any dose level**
- As expected significant toxicity was restricted to myelosuppression
  Reversible Gr 4 neutropenia in 33% and Gr 4 thrombocytopenia in 13.3%

Treatment Emergent Adverse Events
(individual subject's worst grade)

CTCAE v3	Gr 1-2	Gr 3	Gr 4	Total
Non-Hematologic				
Alopecia	5			5 (33.3%)
Bloating	1			1 (6.7%)
Diarrhea	1			1 (6.7%)
Dizziness	1			1 (6.7%)
Dysgeusia	1			1 (6.7%)
Fatigue	3			3 (20%)
Haptoglobin decrease	1			1 (6.7%)
Heartburn	1			1 (6.7%)
Hyperglycemia	1			1 (6.7%)
Hypophosphatemia		1		1 (6.7%)
Muscle weakness	1			1 (6.7%)
Mucositis (oral)	1			1 (6.7%)
Nausea	2			2 (13.3%)
Neuropathy	2			2 (13.3%)
Tremor	1			1 (6.7%)
Hematologic				
Anemia	5			5 (33.3%)
Thrombocytopenia	2	2	2	6 (40%)
Leukopenia	2	8	3	13 (86.7%)
Lymphocytopenia	3	4	4	11 (73.3%)
Neutropenia	1	6	5	12 (80%)

CONCLUSIONS

- The combination of fractionated dose^{177}Lu-J591 and docetaxel/prednisone was well tolerated with metastatic castrate-resistant prostate cancer
- Subjects at the highest anticipated dose level were able to receive 75 mg/m2 of docetaxel q3 weeks (with a 3-wk pause for radioimmunotherapy)
- Without pre-selection for PSMA expression, accurate targeting of known sites of disease and a strong preliminary efficacy signal for the combo was observed

Supported by: Prostate Cancer Foundation; NIH ULI RR024996, 1-KL2-RR024997-01, PTBF5405; Department of Defense PC040566; David H. Koch Foundation

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CDMRP
Department of Defense
Prostate Cancer Research Program

PCRP erspectives

Volume 4, Number 1 – March 2014

In This Issue

Featured Opinion

Robert J. Gillies, Ph.D.
Vice Chair, Radiology
Director, Experimental Imaging Program
Moffitt Cancer Center
PCRP Integration Panel Member

Medical imaging plays a central role in the life of every prostate cancer patient. A positive prostate-specific antigen test is routinely followed up with an imaging session, usually ultrasound, to direct biopsy to suspicious regions of the prostate. More-advanced diseases are generally imaged with magnetic resonance imaging (MRI) or computed tomography. Although imaging has served us well in the past, we are at the advent of a revolution wherein we can not only detect the presence of cancer but can observe how it is behaving metabolically and biochemically. We will see a day when noninvasive imaging has advanced to the point that only required biopsies are obtained and needless biopsies can be avoided.

Over the last few years, advancing prostate imaging has been an explicit focus of the PCRP. As a consequence of this effort, new noninvasive approaches are being developed to interrogate prostate cancers in men, with the goal of developing sensitive and specific imaging tests to detect and monitor disease prior to and during the course

» continued, **SEE OPINION, PG. 6**

PCRP Commitment to Imaging Research

In 2014, more than 233,000 new cases of prostate cancer are estimated to be diagnosed and nearly 30,000 lives will be lost due to the disease.[1] Although prostate cancer is a very serious, potentially lethal disease in its more aggressive forms, most men diagnosed with the disease do not die from it. The prostate cancer community recognizes that overdiagnosis and overtreatment of men with non-life-threatening prostate cancer is highly problematic and that there is a critical need to develop better tools to detect and diagnose only clinically significant prostate cancer. Between 2009 and 2012, the PCRP Integration Panel (IP), consisting of patient advocates, physician scientists, and laboratory researchers, bringing together their dedication to conquering prostate cancer, developed a strategy to more specifically address the critical needs of prostate cancer patients. To that end, the IP initiated the PCRP Overarching Challenges to encourage applicants for PCRP funding to (1) develop better tools to detect clinically relevant disease in asymptomatic men, (2) distinguish aggressive from indolent disease in men newly diagnosed with prostate cancer, and (3) develop effective treatments and address mechanisms of resistance for men with high-risk or metastatic prostate cancer. In addition, to maintain a broad portfolio of research that seeks to better understand and treat prostate cancer using a diversity of approaches, all PCRP-funded research must address at least one of seven PCRP focus areas. Two key focus areas with the ultimate goal

» continued, **SEE COMMITMENT, PG. 4**

PCRP-Funded Investigators in Imaging Research Work toward Improving Prostate Cancer Detection, Diagnosis, and Treatment

In prostate cancer, a recognized need persists to develop an accurate, noninvasive test that can discriminate clinically significant, life-threatening (aggressive) disease from that which is indolent and non-life-threatening. Existing methods of detection, such as elevated blood prostate-specific antigen (PSA) as a marker for prostate cancer, have contributed to overdiagnosis and overtreatment of men with non-life-threatening prostate cancer. In addition, conventional prostate biopsy after detection of elevated PSA may miss as much as 30% of the aggressive forms of prostate cancer.[1] As a result, more-precise imaging procedures are needed to guide prostate biopsies to the most dangerous areas of the tumor and to detect metastatic spread of cancer cells. Moreover, new imaging procedures will assist with better treatment planning for patients with early-stage disease and those with more aggressive prostate cancer, as well as assessing their response to therapy. To that end, the PCRP has funded

» continued, **SEE FUNDED INVESTIGATORS, PG. 2**

VISION: Conquer prostate cancer.

MISSION: Fund research that will lead to the elimination of death from prostate cancer and enhance the well-being of men experiencing the impact of the disease.

» FUNDED INVESTIGATORS CONTINUED FROM PG. 1

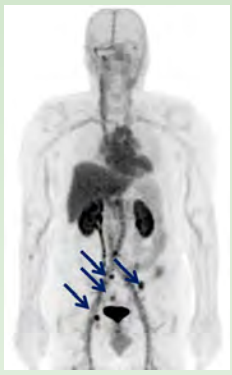
basic, translational, and clinical research by investigators who, using multiple medical imaging technologies, have made major contributions to improving prostate cancer detection, diagnosis, and treatment for the well-being of men with prostate cancer.

During the 1990s, radiation therapy was proven to be curative for most patients with early-stage, localized prostate cancer. However, for some patients, curative doses of radiation therapy were unsuccessful due to the uncertain position of the prostate during treatment. This uncertainty was managed by increasing the size of the radiation field, but this also increased radiation exposure to normal tissues surrounding the prostate, causing unwanted side effects. To address this issue, **Dr. David Jaffray** and colleagues of the Beaumont Health System Research Institute, with PCRP funding from fiscal year 1997 (FY97) and FY00, developed a novel imaging approach to better target radiation to prostate tumors by integrating a computed tomography (CT) technique known as cone-beam CT. Today, this approach is used as the standard for precision radiation treatment of prostate cancer; it enables radiologists to image exact tumor location and then direct curative radiation doses to the prostate. The cone-beam CT imaging approach has proven to be a substantial commercial success—80% of radiation machines sold today are equipped with it.

Dr. David Jaffray

The challenge of developing more-effective treatments for prostate cancer patients has guided the identification of tumor-specific biomarkers—molecules that are expressed on tumor cells but not normal cells in the body—that can be targeted by new therapeutic and molecular imaging technologies. One such example is prostate-specific membrane antigen (PSMA), the focus of **Dr. Neil Bander's** research at Weill Cornell Medical College (WCMC). With multiple PCRP awards spanning FY97 to FY04, Dr. Bander and **Dr. Shankar Vallabhajosula** developed a protein antibody against PSMA, called J591. In preclinical studies using radioactive isotopes (e.g., 111In) linked to J591, the investigators demonstrated the potential for prostate cancer imaging using nuclear medicine techniques in animal models. In subsequent clinical studies of patients with prostate cancer, supported by FY08 PCRP funding, **Dr. Scott Tagawa** (also at WCMC), in collaboration with Dr. Bander's team, demonstrated that imaging with the radiolabeled antibody detected very small, previously undetectable, prostate cancer bone metastases. Currently, radiolabeled J591 imaging is being used in a multi-institutional clinical trial to assess the treatment response in patients with metastatic prostate cancer. Another promising approach targeting PSMA, developed by **Dr. Martin Pomper** of Johns Hopkins University, a FY05 PCRP awardee, uses a small-molecule PSMA binding agent that is attached to a radioactive positron emitting atom (fluorine-18) that can be visualized using a positron emission tomography (PET) scanner. Dr. Pomper demonstrated that this small-molecule PSMA probe originally described by Kozlowski and coworkers could be used to image prostate tumors in animals. Following its success, this technology was patented and then licensed to a pharmaceutical company that went on to develop closely related derivatives, which are currently in Phase II clinical trials to evaluate their utility in imaging prostate cancer metastases in patients.

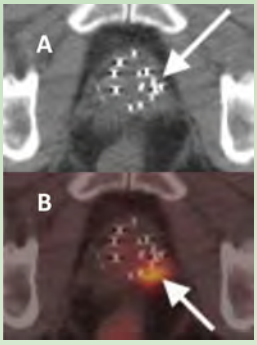
Dr. Martin Pomper



Whole body PET image using [18F]DCFBC shows metastatic prostate cancer (arrows) in a patient (Cho et al., J Nucl Med 2012; 53:1883).

Another molecular imaging approach for cancer, called metabolic imaging, takes advantage of differences in metabolism between cancer and normal cells. Choline is an essential dietary nutrient that is used to make the membranes of normal and cancer cells. With FY04 PCRP funding, **Dr. Sandi Kwee** of Queen's Medical Center in Hawaii, in collaboration with Tripler Army Medical Center and the Armed Forces Institute of Pathology, labeled choline with positron-emitting fluorine-18 (18F-choline) and initiated a clinical trial to evaluate it as a diagnostic PET imaging technique for prostate cancer. Dr. Kwee demonstrated that 18F-choline uptake was consistently increased in malignant prostate tumors as compared with surrounding benign prostate tissue. He provided encouraging evidence for the use of 18F-choline PET imaging to localize more-aggressive areas in primary tumors and detect the spread of more-aggressive cancer cells to metastatic sites in lymph nodes and bone. Referring to 18F-choline PET, Dr. Kwee notes, "One of the most exciting potential applications still being investigated is its use in individualizing cancer treatment, whereby images obtained with PET are used to help plan treatment at the earlier stages and select molecularly targeted therapy at more advanced stages."

Sandi Kwee, MD, PhD (right), along with project co-investigators Marc Coel, MD (middle), and John Lim, PhD (left), in the Cyclotron Laboratory at The Queen's Medical Center.



(A) X-ray computed tomography (CT) image of a patient treated with brachytherapy seed implants (arrow) showing no evidence of cancer. (B) Fluorocholine PET image superimposed on the CT image showing an abnormally high metabolic activity in the prostate (arrow) that was confirmed to be recurrent prostate cancer.

Along this same line of harnessing differences in cancer metabolism to select the most appropriate treatment for a patient, the PCRP has funded several investigators who are using alternative advanced magnetic resonance imaging (MRI)/magnetic resonance spectroscopy (MRS) methods to identify metabolites as biomarkers (e.g., citrate, spermine, choline, creatine) for distinguishing aggressive from indolent prostate cancer. **Dr. Leo Cheng** of the Massachusetts General Hospital, with funding from a FY03 PCRP award, used a specialized diagnostic technique called high-resolution magic-angle spinning MRS to study prostatectomy

Dr. Leo Cheng

» continued, **SEE FUNDED INVESTIGATORS, PG. 5**

In This Issue

Spotlight

Taking Prostate Cancer Personally

Craig Pynn

Author of "One Man's Life-Changing Diagnosis: Navigating the Realities of Prostate Cancer" (Demos Health, 2012)

PCRP Consumer Reviewer

Craig Pynn and his wife Susan

"I knew something was really wrong when I looked down and saw all that blood in the urinal."

So began Craig's journey with high-risk, locally advanced prostate cancer. Shortly after he was diagnosed in January 2009, his urologist told him it was a "nasty, out of the box" cancer. Subsequent tests confirmed that the blood he saw was a direct result of prostate cancer.

"When I was diagnosed, about the only thing I knew about this cancer was that it was pronounced *prostate* and not *prostrate*." The reality of hearing those words no guy ever wants to hear—*you have prostate cancer*—was the same as for every other man: a life-changing diagnosis with a very steep learning curve.

"My journey with this cancer has distinct dimensions—a three-stranded cord, if you will."

First, there's the clinical strand. Since the cancer had already escaped his prostate and invaded his urethra, surgery wasn't an option. "My doctors recommended an aggressive course of treatment, and I'm sure glad they did."

Forty-two sessions of radiotherapy and three years on hormone therapy have resulted in Craig having an undetectable prostate-specific antigen for more than four years.

"But since it escaped my prostate before I was diagnosed, I wake up each morning knowing that one of these days the cancer could come roaring back."

Then, there's what Craig calls the emotional/relational strand. Prostate cancer is rightly called a "couple's disease," and Craig's wife, Susan, has been a loving and supportive partner, knowing too well how hormone therapy affects an intimate relationship. Complicating matters is Susan's own chronic disease, multiple sclerosis.

"We had always assumed that I would be the healthy caregiver," Craig says. "We have learned to love each other more deeply and take it slowly, one day at a time. We give thanks for each new day that we are together."

The third strand is the spiritual dimension. "There is no more effective reminder of your mortality than hearing you have cancer," Craig notes. "I always had a faith in God, but it's not until a serious crisis comes along, and you have to deal with the *Why me?* and *It's so unfair* questions, that you come to know what you really believe."

"When I was diagnosed, I felt really alone. I wanted to know how other men felt. And what they feared."

Craig discovered it wasn't difficult to find men who had been diagnosed and treated for prostate cancer. But they were often unwilling to talk openly about their experience—especially their feelings and their fears. They'd say, "Yes, I had prostate cancer, but I've had surgery and I've moved on. Cancer is in my past."

"So, I went looking for a book written by a man who had prostate cancer that dealt with cancer's psychological and spiritual impact." He found books written by women who had breast cancer that described their emotional battles and spiritual journeys. "I guess few men want to write about how they feel, or what they feared," Craig observes.

"As an engineer, I'm pretty data-driven, so I started scouring the Internet—not just for clinical information but also for men's personal stories. Happily, I found quite a few. And that helped."

Wanting to record his own story, Craig started a journal. "I especially wanted to record my own feelings and fears as I underwent treatment. Eventually, writing became my daily personal therapy."

Craig's journal grew longer as he explored not just his own treatment experience and

» continued, **SEE SPOTLIGHT, PG. 4**

Calendar of Events

April 2014

S	M	T	W	T	F	S
		1	2	3	4	5
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30			

5–9: American Association for Cancer Research (AACR) Annual Meeting 2014, San Diego, CA.
Sponsor: AACR

25: 2014 NCCN Policy Summit: Designing Clinical Trials in the Era of Multiple Biomarkers and Targeted Therapies, Bethesda, MD.
Sponsor: NCCN

May 2014

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16–21: American Urology Association (AUA) Annual Meeting, Orlando, FL.
Sponsor: AUA

June 2014

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18–21: AACR Precision Medicine Series, Drug Sensitivity and Resistance: Improving Cancer Therapy, Orlando, FL.
Sponsor: AACR

August 2014

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31						

31 August–2 September: Asia-Pacific Prostate Cancer Conference, Melbourne, Australia.
Sponsor: Australian Prostate Cancer Research

Did You Know...

- Veterans exposed to the herbicide Agent Orange during military service and who develop prostate cancer do not have to prove a connection between their prostate cancer and military service to be eligible to receive Veterans Affairs health care and compensation.
- Since 2005, the Prostate Cancer Clinical Trials Consortium has developed 156 clinical trials, representing nearly 25% of all early-phase prostate cancer clinical trials, helping to advance ten candidate drugs to Phase III clinical trials and two drugs to U.S. Food and Drug Administration approval.
- Charles Huggins, MD, of the University of Chicago, won the Nobel Prize in Physiology or Medicine in 1966 for work he published in 1941 showing that blocking male hormone production or using estrogen to neutralize male hormones could cause tumor regression in men with metastatic prostate cancer. Dr. Huggins died in 1997, the same year the PCRP was established.

In This Issue

» SPOTLIGHT, CONTINUED FROM PG. 3

feelings, but also widened his research to the demographics, economics, medical controversies, and advocacy issues surrounding prostate cancer.

The journal evolved into a book, *One Man's Life-Changing Diagnosis: Navigating the Realities of Prostate Cancer*, published by Demos Health (New York) in 2012, and winning a "book of the year" citation from the *American Journal of Nursing* in early 2013.

"My passion has become helping guys like me (as the book's title says) navigate the realities of prostate cancer." In addition to counseling newly diagnosed men one-on-one, Craig is active in prostate cancer advocacy, including participating with the advocacy organizations Us Too International, Malecare, and ZERO: The End of Prostate Cancer, the latter of which conducts an annual summit where participants gather in Washington, DC, to advocate for prostate cancer research funding, particularly for the innovation- and impact-based Department of Defense Prostate Cancer Research Program (PCRP), with their own senators and congresspersons.

"My passion is talking with newly diagnosed men and their spouses, and helping them make those decisions I had to make alone," Craig emphasizes. "But equally rewarding has been my privilege to be a Consumer Reviewer for the PCRP. My four years (so far) helping to identify the best research or make a positive difference for men like me have been a fabulous learning experience as I've learned just how enormously complex prostate cancer is, and why it is such a challenge to eradicate this scourge.

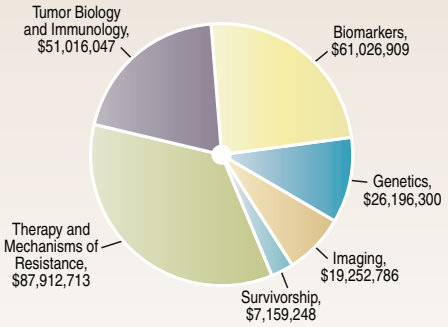
But perhaps the most outstanding aspect of being a Consumer Reviewer has been to meet and work with the dedicated scientists and PCRP staff who are just as passionate about conquering this cancer as we guys who actually have the disease. It is difficult to imagine a more fulfilling way of 'giving back' and helping ensure that the thousands of men who follow me will not only benefit from the terrific work being accomplished by PCRP-funded scientists, but that they will never have to experience those dark fears of feeling so alone when they hear those four awful words, *you have prostate cancer*."

»COMMITMENT CONTINUED FROM PG. 1

of developing better treatment planning for patients with early-stage or aggressive prostate cancers are biomarkers and imaging. In 2013, encouraged by Congress's recognition of the lack of reliable diagnostic tools for guiding early detection and treating prostate cancer, the PCRP resolved to increase the focus on research with near-term clinical impact, with emphasis on the advancement of prostate cancer imaging technologies.

The PCRP has had a longstanding commitment to improving the detection and diagnosis of prostate cancer through imaging technologies, as evidenced by investments in imaging studies dating back to 1997 and representing 210 studies totaling over $80.2 million (M) in PCRP funding. These projects range from exploratory studies aimed at generating highly innovative and cutting-edge new imaging technologies and contrast agents to clinical imaging studies that have the potential to transform prostate cancer clinical care. The following innovation-based award mechanisms[2] have proven to be a successful avenue for supporting imaging advances: Idea Development Award (91), New Investigator Award (42), Exploration - Hypothesis Development Award (16), Synergistic Idea Development Award (10), and Training Awards (43). The accompanying articles—"Featured Opinion," by fiscal year 2013 (FY13) IP member Dr. Robert Gillies, and "PCRP-Funded Investigators in Imaging Research Work Toward Improving Prostate Cancer Detection, Diagnosis, and Treatment," describe imaging projects funded by the PCRP that have led to major advancements for prostate cancer patients, with many ongoing studies in development or in early stages of clinical application.

Since the introduction of the PCRP overarching challenges and focus areas in FY09, the program has supported 49 awards in prostate cancer imaging research representing an investment of more than $19M. These awards have been made to 28 institutions across 19 states. In addition, the PCRP has developed new award mechanisms that focus on clinically relevant near-term investigations with an eye on impacting patient care and addressing the overarching challenge to develop better tools, including those relevant to imaging, for the detection and diagnosis of prostate cancer. The PCRP Biomarker Development Award was introduced in 2012 to fund studies that will advance prostate cancer biomarkers, including those that can be assessed using noninvasive or minimally invasive new imaging technologies or in biofluids (e.g., blood, urine), into the clinical setting. Specifically, this award supports high-impact research aimed at multi-institutional validation and/or qualification of prostate cancer biomarkers for crucial decision-making in prostate cancer management. Also introduced in 2012, the PCRP Transformative Impact Award supports multi-institutional research with near-term clinical relevance such as translational research, clinical research, and/or clinical trials that may include imaging studies, provided they have the potential to make a revolutionary impact on the clinical management of prostate cancer. For these new mechanisms, as with all PCRP awards, researchers must clearly demonstrate the potential of the study to contribute significantly to the elimination of death from prostate cancer and/or enhance the well-being of men experiencing the impact of the disease.



Since its inception in 1997 and over its 17-year history of congressional support, the PCRP has funded a large number of basic, translational, and clinical research studies using medical imaging technologies. The PCRP continues to encourage such applications that take advantage of revolutionary advances in prostate cancer imaging, and it especially seeks applications that address the critical needs of prostate cancer patients.

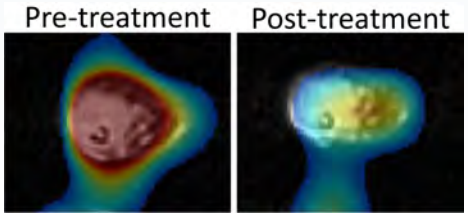
[1] *http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-key-statistics*

[2] *Number of awards made indicated in parentheses.*

» FUNDED INVESTIGATORS CONTINUED FROM PG. 2

samples from prostate cancer patients. He demonstrated that this technique could detect and accurately differentiate cancerous from benign areas of the prostate. In addition, these metabolomic profiles distinguished a subset of less-aggressive tumors and predicted invasive cancer in moderately aggressive (Gleason score 6 or 7) tissues. Moreover, **Dr. Michael Albert Thomas** and coworkers at the University of California, Los Angeles, are developing another specialized multi-dimensional MRS imaging technique with funding from PCRP awards (FY04 and FY10) to monitor prostate metabolites. In this ongoing study, men undergo prostate imaging using an endorectal coil, and those with malignant prostate cancer are compared to their healthy counterparts. Using this novel technique, Dr. Thomas has shown that MRS images can detect prostate cancer features that correlate with Gleason score and may help to distinguish aggressive from indolent prostate cancer. **Dr. Sabrina Ronen** of the University of California, San Francisco, with support from an FY06 PCRP award, focused on testing new MRI methods to monitor responses to prostate cancer bone metastasis treatment. Using animal models, she demonstrated that two different MRI methods, dynamic contrast enhanced MRI and hyperpolarized 13C MRS, can be used to monitor decreases in the blood supply to tumors in the bone and decreases in the metabolic conversion of pyruvate into lactate in response to a conventional cytotoxic drug (paclitaxel) and molecular therapy targeting the tumor vasculature (imatinib), respectively. These methods are currently being used in ongoing clinical trials to determine if prostate cancer patients are responding to treatment.

Dr. Sabrina Ronen



Metabolic imaging of a prostate cancer bone metastasis in a mouse prior to and following 2 days of imatinib treatment showing a drop in the intensity of hyperpolarized lactate produced from hyperpolarized pyruvate.

Another imaging approach that holds promise for detection of aggressive prostate cancer is ultrasound. **Dr. Ethan Halpern** of Thomas Jefferson University was funded by the PCRP between FY00 and FY05 to study intermittent ultrasound using a micro-bubble contrast agent in patients in hopes of improving the detection of prostate cancer during prostate biopsies. He showed that contrast-enhanced ultrasound provided a significant improvement in discriminating between benign and malignant areas within the prostate. This technique improves a clinician's ability to detect malignant areas of the prostate, thereby reducing the need for repeated biopsies and providing a more accurate assessment of the aggressiveness of the disease. In a subsequent study, Dr. Halpern went on to show that contrast-enhanced ultrasound-guided biopsy significantly improves detection of high-grade prostate cancer (Gleason score 7 or greater). He notes, "Although these contrast-enhanced ultrasound techniques are not perfect, they provide the best available real-time technique for discriminating patients with clinically significant prostate cancer and can provide an additional level of reassurance that their prostate might be safely followed with active surveillance."

Dr. Ethan Halpern

As these medical imaging studies show, scientists and clinicians funded by the PCRP are developing and testing more precise imaging technologies that have already led to major contributions to the care of prostate cancer patients and are likely to continue to improve the detection, diagnosis, and treatment of men with prostate cancer.

[1] *Freedland SJ, Kane CJ, Amling CL, et al. 2007. Upgrading and downgrading of prostate needle biopsies: Risk factors and clinical implications.* Urology *69(3):495–499.*

For more information:
http://cdmrp.army.mil/pcrp/default.htm
General questions:
Phone: (301) 619-7071
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Phone: (301) 682-5507
E-mail: help@cdmrp.org
Consumer involvement:
Phone: (301) 619-7071
E-mail: usarmy.detrick.medcom-cdmrp.mbx.cdmrp-public-affairs@mail.mil

Program News

- In April 2013, the PCRP established an aggressive timeline to execute the $80 million appropriated by Congress for fiscal year 2013 (FY13). Peer and programmatic reviews for 1,115 compliant applications to the PCRP were completed by February 2014.
- Maha Hussain, MD, FACP, Professor of Internal Medicine and Urology, Associate Director for Clinical Research, and Co-Leader of the Prostate Cancer and Genitourinary Oncology Program at the University of Michigan Comprehensive Cancer Center, will conclude her service as Chair of the PCRP Integration Panel in March 2014. Philip M. Arlen, MD, President, Chief Medical Officer, and Chief Executive Officer of Precision Biologics, Inc., will assume the chairmanship at the FY14 Vision Setting meeting.
- Brief details for the anticipated FY14 opportunities will be provided in late March on the CDMRP website at http://cdmrp.army.mil/pubs/press/2014/14pcrppreann.shtml (link to be activated in late March).
- Important information for FY14 PCRP applicants: The CDMRP eReceipt System is being phased out and the new electronic Biomedical Research Application Portal (eBRAP) will be used for all FY14 applications. Principal Investigators (PIs) are encouraged to register in eBRAP as soon as possible and allow additional time to become familiar with differences from eReceipt. Importantly, eBRAP will allow PIs to view their applications after submission through Grants.gov so that any needed modifications may be made prior to peer review of the applications.
- Since 2009, the PCRP-funded Prostate Cancer Biorepository Network (PCBN) has developed a sizable collection of high-quality human prostate cancer biospecimens, including 16 tissue microarrays for testing biomarkers associated with various factors such as grade/stage of cancer (200 cases), prostate cancer progression (726 cases), racial disparity (150 cases), and family history (343 cases). The PCBN is making these resources available to the prostate cancer community to support studies focused on the PCRP overarching challenges.

» FEATURED OPINION, CONTINUED FROM PG. 1

of therapy. Positron emission tomography (PET) commonly employs a radioactive sugar analog called 18-F deoxyglucose (FDG) to visualize a number of cancers in the human body. For various reasons, FDG does not work well in prostate cancer, so there has been a concerted effort, funded by the PCRP, to develop newer tracers that have high sensitivity and specificity for prostate cancer. These have included radiolabeled choline, which is more rapidly taken up and metabolized by aggressive prostate cancers. Even more specificity can be found with tracers that are targeted to cell surface receptors expressed in prostate cancers and not normal tissues, such as prostate-specific membrane antigen. These tracers can be used to detect cancer in the prostate gland and metastases, which is critical to the evaluation of therapy against advanced disease.

MRI is a nonradioactive technique with exquisite sensitivity to image multiple components of cancers in the same session. Hence, multiparametric MRI (mp-MRI) is commonly used to initially diagnose as well as monitor men who are on active surveillance or active treatment. The PCRP has funded researchers to expand the number of parameters available to mp-MRI scans, including multiple metabolic intermediates such as choline, citric acid, and certain lipids that are powerful biomarkers for aggressive disease. More recently, with support from the PCRP, a new MRI technique called hyperpolarized MRI is being developed that uses metabolic substrates, such as pyruvic acid, that are hyperpolarized, which increases their detectability greater than 10,000-fold. Pyruvic acid is converted rapidly to lactic acid in aggressive prostate cancers, and this conversion can be measured noninvasively.

The most common imaging technique performed in prostate cancer surveillance is ultrasound; over the past few years, the PCRP has promoted the development of photoacoustic tomography, a new technique using a pulse of light to stimulate specific dyes, which then heat up slightly to generate a signal that can be detected by an ultrasound machine. This is a very powerful approach because, as with PET and MRI, these dyes can be specifically targeted to prostate cancers where they can be readily detected.

In all, the PCRP, through its strategic vision, is contributing greatly to the revolution in prostate cancer imaging, and these advancements will greatly impact and improve the management of this disease.

Summary of FY12 and FY13 Awards

Award Mechanisms by Emphasis	FY12 Awards Made	FY13 Awards Recommended
Impact		
Biomarker Development	0	Award TBD*
Clinical Exploration	1	Not offered in FY13
Health Disparity Research	6	5
Laboratory - Clinical Transition	2	1
Population-Science Impact	Not offered in FY12	0
Transformative Impact	3	Award TBD*
Innovation		
Exploration - Hypothesis Development	31	20
Idea Development Award - Established Investigator	21	26
Idea Development Award - New Investigator	8	12
Synergistic Idea Development	13 (6 projects)	14 (6 projects)
Training		
Collaborative Undergraduate HBCU Student Summer Training Program	5	4
Physician Research Training	5	3
Postdoctoral Training	30	22
Resources		
Clinical Consortium	Not offered in FY12	Award TBD*
Prostate Cancer Pathology Resource Network	Not offered in FY12	Award TBD*

*To be determined

To subscribe to this free newsletter, please contact the editor at perspectives@cdmrp.org.

Grant Writing Tips

- The majority of applications are submitted on the submission deadline date. **Earlier submissions allow time** for Grants.gov and eBRAP [electronic Biomedical Research Application Portal] to process the application, and **for the Principal Investigator to make any modifications** so that the application has the best chances of success!
- It is very important that applicants thoroughly **read the Program Announcement before preparing applications.** Although award mechanism names usually remain the same from year to year, there may be significant changes made each year to the application requirements.
- **A well-written grant application is easy to read AND understand!** After presenting your ideas in a clear, descriptive, and specific manner, have a few people in your field (but not working on efforts close to your specific projects) read your pre-application or application, and get honest opinions on its readability. If your readers hesitate in telling you how clear and easy it is to understand, challenge yourself to rewrite until you've achieved maximum clarity!
- Ensure that your hypothesis, broad objectives, and specific aims clearly demonstrate **significant relevance to prostate cancer** and PCRP goals.

Watch for more tips in the next issue!

Visit the PCRP Webpage for Up-to-Date Program Information

The DoD PCRP supports innovative ideas and technologies to accelerate our vision to conquer prostate cancer through individual, multidisciplinary, and collaborative research. These efforts are focused toward basic research discoveries and translating discoveries into clinical practice to improve the quality of care and life of men with prostate cancer. For more information on PCRP initiatives, highlights of funded research, and consumer profiles, please visit

http://cdmrp.army.mil/pcrp/default.shtml

In This Issue

Weill Cornell Medical College

Rosemary Kraemer, Ph.D.
Director, Human Research Protections Programs
Office of Research Integrity
407 East 61st Street, First Floor
New York, New York 10065

Telephone: 646-962-8200
Email: irb@med.cornell.edu

November 25, 2013

Scott T. Tagawa, MD

Submission Type:	Continuing Review with Amendment
Protocol Number:	0810010067 R005
Protocol Title:	A Randomized Phase 2 Trial of Lu Radiolabeled Monoclonal Antibody HuJ591 (Lu-J591) and ketoconazole in Patients with High-Risk Castrate Biochemically Relapsed Prostate Cancer After Local Therapy.
Status of IRB Protocol:	Open
Risk Level:	Greater than Minimal
Nature of Amendment:	Submission of Sponsor Protocol, version 7 dated October 31, 2013 Removal of co-investigator: Lilja Solnes Addition of co-investigators: David Mozley & Yuliya Jhanwar

Dear Dr. Tagawa:

The renewal for the abovementioned protocol was reviewed at the November 20, 2013 meeting of the Institutional Review Board (Cancer IRB 2).

The protocol and its relevant documents stand approved for the following period:

- Revised Informed Consent Form, version date October 31, 2013
- Sponsor's Protocol, version 7 dated October 31, 2013
- FACT-P Questionnaire
- Subject Brochure
- Subject Information Sheet
- Cumulative deviation log
- Cumulative IND/SAE safety table
- Publication from Frontiers in Oncology, dated 08.26.13
- DSMB outcome letter for periodic review, dated 09.20.13
- FDA Annual Report, submitted to the FDA on 10.24.12

Approved: November 20, 2013 **Expires**: November 19, 2014

Please do not hesitate to contact the IRB office staff if you have any questions or need assistance in complying with the terms of this approval.

Sincerely,

Rosemary Kraemer

Rosemary Kraemer, Ph.D.
Director, Human Research Protections Program

Please note the following important information about this approval:

- Billing Compliance: This approval is contingent upon continued adherence with institutional billing compliance policies.
- Immediate Reporting: Investigators must follow the Immediate Reporting Policy at http://weill.cornell.edu/research/rea_com/irb_adv.html Failure to comply with IRB directives within specified time frames may result in federally mandated penalties, up to and including suspension or termination of IRB approval and mandatory reporting to the Federal government.
- Other reporting: The reporting requirements of various regulatory bodies may differ with regard to both what must be reported and when. You are responsible for acquainting yourself with and abiding by all applicable federal and state regulatory reporting requirements.
- Changes to this protocol: If you want to change this research in any way or if any unanticipated hazardous conditions emerge affecting the rights or welfare of the human subjects involved in it, you must submit an amendment detailing these changes to the IRB for review and approval prior to implementing those changes. If the CTSC is used, the changes must also be submitted to the Translational Research Advisory Committee (TRAC). It is your responsibility to obtain approval for any such changes prior to initiating them.
- Continuing approval: You will receive a reminder via email for continuing review of this protocol in advance of the expiration date. The continuing review forms must be filed with the IRB sufficiently early to permit timely review and approval if the project is to continue beyond the period for which it was approved. Please note, no study related activities can continue beyond the WCMC IRB expiration date, including subject recruitment, enrollment, intervention and data analysis.
- If your research study involves human tissues: In addition to IRB approval, Section 4.4 of the hospital By-Laws **"Specimens Removed During Resective Surgery"** requires that all specimens removed during surgical diagnostic procedures that will be used for research must be approved by Pathology Service. Information about Pathology review can be found online at http://www.med.cornell.edu/research/for_pol/forms/Pathology_Review_Instructions.pdf
- If the IRB is requiring that you obtain informed consent from subjects: The signed IRB approved consent forms must be kept in the subject's hospital chart. If the subject has no New York Presbyterian Hospital chart, you are responsible for retaining such signed forms in your research files.
- Information about the WCMC IRBs: The Weill Cornell Medical College (WCMC) Institutional Review Board (IRB) is constituted as required by the Federal Office for Human Research Protections (OHRP). WCMC holds a Federalwide Assurance (FWA) with OHRP. The FWA number is FWA00000093. The WCMC IRB is registered on that FWA. The registration number for the IRB is: General IRB #1 IRB00009417, General IRB #2 IRB00009418, Cancer IRB#1 IRB00009420, Cancer IRB#2 IRB00009421 and Expedited IRB IRB00009419. Should you need additional information about the terms of the WCMC FWA or the WCMC IRBs, please refer to http://weill.cornell.edu/research/research_integrity/institutional_review_board/index.html.
- Note that new federal legislation took effect April 7, 2008, (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-033.html), requiring that all peer-reviewed journal articles resulting from NIH supported research be deposited in PubMed Central, the NIH free digital archive of biomedical and life sciences journal literature, and be made publicly available within twelve months of publication. The Library and RASP have prepared general information which you can see at: http://library2.med.cornell.edu/FacPub/nihpolicy.html
- The International Committee of Medical Journal Editors (ICMJE) has established a requirement that all clinical trials be entered in a public registry before the onset of patient enrollment as a condition of

consideration for publication. Additional information may be found at http://clinicaltrials.gov/ and at http://www.icmje.org/clin_trialup.htm Please contact the Protocol Registration System ("PRS") administrator by e-mail at octa@med.cornell.edu to set up a PRS user account to register new and ongoing investigator-initiated clinical trials. The e-mail should contain the PIs full name, department, phone number and e-mail address.